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-	372	BIR$5 WITH domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/14 16:10
-	39	(BIR$5 WITH domain) and iap	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/14 16:10
-	27	Robert WITH KORNELUK,	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 14:50
-	25	(XIAP M-XIAP HIAP$3 M-HIAP$3) SAME BIR$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 15:39
-	1	("6511828").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 15:40
-	2	("6245523").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 15:40
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-	2	("6187557").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/05 18:02

(FILE 'HOME' ENTERED AT 17:38:19 ON 01 MAY 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 17:38:55 ON 01 MAY 2003

L1 0 S INHIBITOR OF APOPTOSIS PROTIEN
L2 1411 S INHIBITOR OF APOPTOSIS PROTEIN
L3 184 S L2 AND BIR?
L4 46 S L3 AND (BIRIII OR BIR-III OR BIR3 OR BIR-3)
L5 21 DUP REM L4 (25 DUPLICATES REMOVED)
L6 21 FOCUS L5 1-

=> d an ti so au ab l6 1 4 6 10 11 21

L6 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2003 ACS
AN 2003:58269 CAPLUS
DN 138:120454
TI Identification of Omi/HtrA2 as a mitochondrial apoptotic serine proteinase that disrupts **inhibitor** of **apoptosis protein** -caspase interaction and its therapeutic use
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
IN Alnemri, Emad S.
AB An isolated nucleic acid mol. comprising a polynucleotide having a sequence encoding a peptide or polypeptide of Omi having at least an N-terminus amino acid sequence of Ala-Val-Pro-Ser which is capable of specifically binding to at least a portion of an **Inhibitor** of **Apoptosis protein**. The mature serine protease Omi (also known as HtrA2) was identified as a mitochondrial direct baculoviral **inhibitor** of **apoptosis protein** (IAP) repeat 3 (**BIR3**) domain-binding protein and a caspase activator. Mature Omi contains a conserved IAP-binding motif (AVPS) at its N terminus, which is exposed after processing of its N-terminal mitochondrial targeting sequence upon import into the mitochondria. Mature Omi is released together with mature Smac from the mitochondria into the cytosol upon disruption of the outer mitochondrial membrane during apoptosis. Finally, mature Omi can induce apoptosis in human cells in a caspase-independent manner through its protease activity and in a caspase-dependent manner via its ability to disrupt caspase-IAP interaction. Our results provide clear evidence for the involvement of a mitochondrial serine protease in the apoptotic pathway, emphasizing the crit. role of the mitochondria in cell death. This peptide can be used in a method to modulate apoptosis or to identify modulators of apoptosis as well as in therapeutic uses.

L6 ANSWER 4 OF 21 MEDLINE
AN 2001038264 MEDLINE
TI NMR structure and mutagenesis of the third **Bir** domain of the **inhibitor** of **apoptosis protein** XIAP.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 27) 275 (43) 33777-81.
Journal code: 2985121R. ISSN: 0021-9258.
AU Sun C; Cai M; Meadows R P; Xu N; Gunasekera A H; Herrmann J; Wu J C; Fesik S W
AB The **inhibitor** of **apoptosis proteins** (IAPs) regulate the caspase family of cysteine proteases, which play an important role in the execution of programmed cell death. Human X-linked **inhibitor** of **apoptosis protein** (XIAP) is a potent inhibitor of caspases-3, -7, and -9. Here we show that the **Bir3** domain is the minimal region of XIAP that is needed for potent caspase-9 inhibition. The three-dimensional structure of the **Bir3** domain of XIAP, determined by NMR spectroscopy, resembles a classical zinc finger and consists of five alpha-helices, a three-stranded beta-sheet, and a zinc atom chelated to three cysteines and one histidine. The structure of the **Bir3** domain is similar to that of the **Bir2** domain of XIAP but differs from the previously determined structure of the **Bir3** domain of MIHB. Based on site-directed mutagenesis, we have identified the regions of the **Bir3** domain of XIAP that are important for inhibiting caspase-9. Despite the structural similarities of the **Bir2** and **Bir3** domain of XIAP, a different set of residues were found to be critical for inhibiting the individual caspases. These results suggest that XIAP inhibits caspase-3 and caspase-9 in a different manner.

L6 ANSWER 6 OF 21 MEDLINE
AN 1999438002 MEDLINE
TI Cleavage of human **inhibitor** of **apoptosis protein** XIAP results in fragments with distinct specificities for caspases.
SO EMBO JOURNAL, (1999 Oct 1) 18 (19) 5242-51.
Journal code: 8208664. ISSN: 0261-4189.
AU Deveraux Q L; Leo E; Stennicke H R; Welsh K; Salvesen G S; Reed J C
AB Several human inhibitor of apoptosis (IAP) family proteins function by directly inhibiting specific caspases in a mechanism that does not require IAP cleavage. In this study, however, we demonstrate that endogenous XIAP is cleaved into two fragments during apoptosis induced by the tumor necrosis factor family member Fas (CD95). The two fragments produced comprise the baculoviral inhibitory repeat (**BIR**) 1 and 2 domains (**BIR1**-2) and the **BIR3** and RING (**BIR3**-Ring) domains of XIAP. Overexpression of the **BIR1**-2 fragment inhibits Fas-induced apoptosis, albeit at significantly reduced efficiency compared with full-length XIAP. In contrast, overexpression of the **BIR3** -Ring fragment results in a slight enhancement of Fas-directed apoptosis. Thus, cleavage of XIAP may be one mechanism by which cell death programs circumvent the anti-apoptotic barrier posed by XIAP. Interestingly, ectopic expression of the **BIR3**-Ring fragment resulted in nearly complete protection from Bax-induced apoptosis. Use of purified recombinant proteins revealed that **BIR3**-Ring is a specific inhibitor of caspase-9 whereas **BIR1**-2 is specific for caspases 3 and 7. Therefore XIAP possesses two different caspase inhibitory activities which can be attributed to distinct domains within XIAP. These data may provide an explanation for why IAPs have evolved with multiple **BIR** domains.

L6 ANSWER 10 OF 21 MEDLINE
AN 1998192555 MEDLINE
TI A single **BIR** domain of XIAP sufficient for inhibiting caspases.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Apr 3) 273 (14) 7787-90.
Journal code: 2985121R. ISSN: 0021-9258.
AU Takahashi R; Deveraux Q; Tamm I; Welsh K; Assa-Munt N; Salvesen G S; Reed J C
AB The **inhibitor** of **apoptosis proteins** (IAPs) constitute an evolutionarily conserved family of homologous proteins that suppress apoptosis induced by multiple stimuli. Some IAP family proteins, including XIAP, cIAP-1, and cIAP-2, can bind and directly inhibit selected caspases, a group of intracellular cell death proteases. These caspase-inhibiting IAP family proteins all contain three tandem **BIR** domains followed by a RING zinc finger domain. To determine the structural basis for caspase inhibition by XIAP, we analyzed the effects of various fragments of this IAP family protein on caspase activity in vitro and on apoptosis suppression in intact cells. The RING domain of XIAP failed to inhibit the activity of recombinant caspases-3 or -7, whereas a fragment of XIAP encompassing the three tandem **BIR** domains potently inhibited these caspases in vitro and blocked Fas (CD95)-induced apoptosis when expressed in cells. Further dissection of the XIAP protein demonstrated that only the second of the three **BIR** domains (**BIR2**) was capable of binding and inhibiting these caspases. The apparent inhibition constants (Ki) for **BIR2** -mediated inhibition of caspases-3 and -7 were 2-5 nM, indicating that this single **BIR** domain possesses potent anti-caspase activity. Expression of the **BIR2** domain in cells also partially suppressed Fas-induced apoptosis and blocked cytochrome c-induced processing of caspase-9 in cytosolic extracts, whereas **BIR1** and **BIR3** did not. These findings identify **BIR2** as the minimal caspase-inhibitory domain of XIAP and indicate that a single **BIR** domain can be sufficient for binding and inhibiting caspases.

L6 ANSWER 11 OF 21 MEDLINE
AN 2002303430 MEDLINE
TI Molecular targeting of **inhibitor** of **apoptosis proteins** based on small molecule mimics of natural binding partners.
SO BIOCHEMISTRY, (2002 Jun 11) 41 (23) 7344-9.

Journal code: 0370623. ISSN: 0006-2960.

AU Kipp Rachael A; Case Martin A; Wist Aislyn D; Cresson Catherine M; Carrell Maria; Griner Erin; Wiita Arun; Albiniak Philip A; Chai Jijie; Shi Yigong; Semmelhack Martin F; McLendon George L

AB An assay based on a solvent-sensitive fluorogenic dye molecule, badan, is used to test the binding affinity of a library of tetrapeptide molecules for the **BIR3** (baculovirus IAP repeat) domain of XIAP (X-linked **inhibitor** of **apoptosis protein**). The fluorophore is attached to a tetrapeptide, Ala-Val-Pro-Cys-NH(2), through a thiol linkage and, upon binding to XIAP, undergoes a solvatochromic shift in fluorescence emission. When a molecule (e.g., a natural protein known to bind to XIAP or a tetrapeptide mimic) displaces the dye, the emission shifts back to the spectrum observed in water. As emission intensity is related to the binding of the tetrapeptide, the intensity can be used to determine the equilibrium constant, K, for the displacement of the dye by the tetrapeptide. The results permit residue-specific analysis of the interaction. Furthermore, we show that hydrophobic effects in the fourth position are general and can effectively increase overall affinity.

L6 ANSWER 21 OF 21 MEDLINE

AN 2002075834 MEDLINE

TI Sequence requirements for Hid binding and apoptosis regulation in the baculovirus inhibitor of apoptosis Op-IAP. Hid binds Op-IAP in a manner similar to Smac binding of XIAP.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 25) 277 (4) 2454-62. Journal code: 2985121R. ISSN: 0021-9258.

AU Wright Casey W; Clem Rollie J

AB It has been suggested that the Drosophila Hid protein interacts with the baculovirus Op-IAP protein in a manner similar to that of human Smac binding to XIAP, based largely on amino acid sequence homology. However, there is little direct experimental evidence in support of this hypothesis; indeed, evidence exists from previous studies suggesting that the mode of binding is not similar. We have now precisely mapped the interaction between Hid and Op-IAP, and we show clearly for the first time that the biochemical interactions between the amino terminus of Hid and **BIR2** of Op-IAP are highly similar to those found between the processed amino terminus of Smac and **BIR3** of XIAP. Also similar to Smac, the amino terminus of Hid must be processed to bind Op-IAP. In addition, our data also suggest that a second interaction between Hid and Op-IAP exists that does not involve the amino terminus of Hid, which may explain some of the earlier contradictory results. The evolutionary conservation of this mechanism of binding underscores its importance in apoptotic regulation. Nevertheless, interaction with Hid is not sufficient for Op-IAP to inhibit apoptosis induced by Hid overexpression or by treatment with actinomycin D, indicating that additional sequence elements are required for the anti-apoptotic function of Op-IAP.

=>

1: 1G73C. Chain C, Crystal ...[gi:13096729] BLink, Domains, Links

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SOURCE      Homo sapiens (human)
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            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 121)
  AUTHORS   Wu,G., Chai,J., Suber,T.L., Wu,J.W., Du,C., Wang,X. and Shi,Y.
  TITLE     Structural basis of IAP recognition by Smac/DIABLO
  JOURNAL   Nature 408 (6815), 1008-1012 (2000)
  MEDLINE   21020962
   PUBMED   11140638
REFERENCE   2  (residues 1 to 121)
  AUTHORS   Wu,G., Chai,J., Suber,T.L., Wu,J.W. and Shi,Y.
  TITLE     Direct Submission
  JOURNAL   Submitted (08-NOV-2000)
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May 1 2003 16:27:42

☐ 1: AAC50373. X-linked inhibito...[gi:1184320] BLink, Domains, Links

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DEFINITION  X-linked inhibitor of apotosis protein.
ACCESSION   AAC50373
VERSION     AAC50373.1  GI:1184320
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KEYWORDS    .
SOURCE      Homo sapiens (human)
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            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 497)
  AUTHORS   Liston,P., Roy,N., Tamai,K., Lefebvre,C., Baird,S.,
            Cherton-Horvat,G., Farahani,R., McLean,M., Ikeda,J., MacKenzie,A.
            and Korneluk,R.G.
  TITLE     Suppression of apoptosis in mammalian cells by NAIP and a related
            family of IAP genes
  JOURNAL   Nature 379 (6563), 349-353 (1996)
  MEDLINE   96149249
   PUBMED   8552191
REFERENCE   2  (residues 1 to 497)
  AUTHORS   Baird,S.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (16-JAN-1996) Stephen D. Baird, Children's Hospital of
            Eastern Ontario, Genetics, 401 Smyth Rd., Ottawa, Ontario, K1H 8L1,
            Canada
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